Adjuvant Radiotherapy and Risk of Contralateral Breast Cancer

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Background: **The risk of contralateral breast cancer is increased twofold to fivefold for breast cancer patients. A registry-based cohort study in Denmark suggested that radiation treatment of the first breast cancer might increase the risk for contralateral breast cancer among 10-year survivors.** ***Purpose:*** **Our goal was to assess the role of radiation in the development of contralateral breast cancer.** ***Methods:*** **A nested case-control study was conducted in a cohort of 56540 women in Denmark diagnosed with invasive breast cancer from 1943 through 1978. Case patients were 529 women who developed contralateral breast cancer 8 or more years after first diagnosis. Controls were women with breast cancer who did not develop contralateral breast cancer. One control was matched to each case patient on the basis of age, calendar year of initial breast cancer diagnosis, and survival time. Radiation dose to the contralateral breast was estimated for each patient on the basis of radiation measurements and abstracted treatment information. The anatomical position of each breast cancer was also abstracted from medical records.** ***Results:*** **Radiotherapy had been administered to 82.4% of case patients and controls, and the mean radiation dose to the contralateral breast was estimated to be 2.51 Gy. Radiotherapy did not increase the overall risk of contralateral breast cancer (relative risk = 1.04; 95% confidence interval = 0.74-1.46), and there was no evidence that risk varied with radiation dose, time since exposure, or age at exposure. The second tumors in case patients were evenly distributed in the medial, lateral, and central portions of the breast, a finding that argues against a causal role of radiotherapy in tumorigenesis.** ***Conclusions:*** **The majority of women in our series were perimenopausal or postmenopausal (53% total versus 38% premenopausal and 9% of unknown status) and received radiotherapy at an age when the breast tissue appears least susceptible to the carcinogenic effects of radiation. Based on a dose of 2.51 Gy and estimates of radiation risk from other studies, a relative risk of only 1.18 would have been expected for a population of women exposed at an average age of 51 years. Thus, our data provide additional evidence that there is little if any risk of radiation-induced breast cancer associated with exposure of breast tissue to low-dose radiation (e.g., from mammographic x rays or adjuvant radiotherapy) in later life. [J Natl Cancer Inst 84:1245–1250, 1992]**

A number of studies have established that exposure of breast tissue to high-dose radiation is a causal factor in the subsequent development of breast cancer. An increased incidence of breast cancer has been observed among atomic bomb survivors *(1),* among women receiving radiation therapy for acute postpartum mastitis *(2)* and benign breast disease *(3),* and among tuberculosis patients receiving multiple fluoroscopic chest examinations *(4).* The age of exposure and the radiation dose absorbed within the breast tissue are important determinants of future risk.

The effect of exposure of breast tissue to low-dose radiation has also been raised as a matter of concern *(5),* particularly with regard to mammographic screening of asymptomatic women for the early detection of breast cancer *(6-9).* In addition, it has been suggested that radiation treatment for primary breast cancer may contribute to the high risk of cancer development in the contralateral breast *(10),* which typically receives between 1 and 3 Gy of incidental and scattered radiation *(11,12).* Minimal surgery (e.g., lumpectomy and axillary dissection or sampling) *(13-15)* with adjuvant radiotherapy *(16)* is now a common treatment strategy for women with small primary breast cancer. The residual tissue in the preserved breast receives approximately 50 Gy *(17),* whereas the contralateral breast may receive a dose of several grays *(18).* Current treatments, however, result in lower radiation doses to the opposite breast than those commonly used in the past.

A population-based cohort study of contralateral breast cancer in Denmark suggested a link with prior radiotherapy, but the radiation doses administered to each patient were not available for analysis *(19).* To assess the possible role of radiation in the development of contralateral breast cancer, we have conducted a case-control study in which we collected individual radiotherapy data for an estimation of dose to the contralateral breast.

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Subjects and Methods

Study Population

Case patients (n = 691) and controls (n = 691) were selected from a cohort of 56540 women with primary breast cancer who were entered in the Danish Cancer Registry from 1943 through 1978. Case patients were women who developed a second primary breast cancer at least 8 years after the diagnosis of the first cancer and who had no other form of cancer in the interim. Controls were women with breast cancer who did not develop a second primary breast cancer in a comparable length of time. Controls were identified and matched to case patients on the basis of age (±5 years), calendar year of first breast cancer diagnosis (±5 years), survival for at least as long as the interval between the first and second diagnosis of breast cancer for the corresponding case patient, and absence of a second primary cancer other than a nonmelanoma skin cancer.

Record Abstraction

For each patient, we obtained surgical and radiotherapy records from the hospitals that treated the primary breast cancer. Radiotherapy records were photocopied and sent to the collaborating dosimetrist. A detailed medical abstract was completed for all case patients and controls. The abstract included the variables listed in Table 1 and details of any benign breast tumor history prior to the first breast cancer. Menopausal status was coded as proposed by the Danish Breast Cancer Cooperative Group *(20);* i.e., perimenopausal status was defined as the first 5 years after a woman reported cessation of regular menstruation. For case patients, we obtained hospital records on the second breast cancer to confirm the histopathology and the position of the tumor in the second breast and to confirm the dates of diagnosis recorded in the cancer registry records. We did not conduct a histopathological review.

Records for the primary breast cancer could not be located for 51 case patients and 89 controls. In addition, 63 case patients and 38 controls were excluded because they had developed another cancer prior to their initial breast cancer (45%), because the latency criteria were not fulfilled (44%), or for other reasons (11%). After we made these exclusions, 135 abstracted eligible case patients were without a control and 142 controls were without a case patient. Rematching of case patients to available controls was then carried out following the same matching criteria as before. If more than one control qualified as a match, a single control was chosen at random. A total of 107 case patients were rematched by this procedure. Of the original 1382 patients, 162 case patients and 162 controls were excluded, leaving 1058 patients available for analysis.

Radiation Dosimetry

Radiation treatment for breast cancer was primarily postoperative and was administered using the method described by McWhirter *(21,22).* Radiation dose to the contralateral breast was reconstructed by placing dosimeters in a female Alderson anthropomorphic phantom *(23).* A cobalt-60 unit, a 6-mV linear accelerator, and an orthovoltage x-ray machine (3-mm Cu half-value layer) were used to simulate actual treatment conditions. Doses from other radiotherapy—for metastases and for prior benign conditions—were calculated on the basis of out-of-beam measurements in a water phantom; however, these other sources of breast irradiation did not appreciably change the estimated dose to the contralateral breast. For each patient, the average dose to the contralateral breast for the primary treatment (i.e., within the 1st year of follow-up) was estimated on the basis of the radiation measurements and the abstracted treatment information. All patients were assumed to be the size of the Alderson phantom, which simulates an average adult female *(23).*

A quality score was assigned for each patient. This score indicated the source and the completeness of information on radiotherapy. Irrespective of case-control status, the dosimetry information was inadequate for only 2% of the patients and was good or adequate for 69%. The estimated mean dose to the contralateral breast among irradiated patients with good or adequate scores was 2.47 Gy. For 29% of the women who received radiotherapy, treatment details were estimated from the records of patients with a similar diagnosis who were treated in the same hospitals. The mean radiation dose calculated from this estimation procedure was 2.58 Gy, a value similar to that obtained when the radiotherapy information was considered good or adequate.

Analysis and Statistical Methods

Conditional logistic regression methods were used to compare radiation exposure in case patients and individually matched controls *(24).* The computer program SAS (MCSCRAT) was used to provide estimates of relative risk (RR) and the corresponding 95% confidence intervals (CIs) based on the asymptotic variance of the estimated RR. Radiation doses to the contralateral breast within the 1st year after breast cancer diagnosis were grouped into categories, and the risks for each category relative to the nonexposed reference category were computed. Dose data classified as "inadequate" were included in the dose–response analysis in a separate category designated "dose unknown." Similarly, patients for whom radiotherapy status was unknown were included in a category called "missing information." The modifying effect that age at exposure might have on any radiation-associated change in risk was analyzed by dividing women into three age groups—less than 45 years old, 45-54 years old, and 55 years old or older. The influence of time since exposure on radiation-associated risk was evaluated by analyzing three latency intervals (8-14 years, 15-19 years, and >=20 years).

Multivariate analyses were conducted to evaluate possible breast cancer risk factors, such as family history of breast cancer, parity, and body mass index. Endocrine therapy (castration excluded) and chemotherapy were also evaluated. For missing values, an additional "unknown" category was included in the analysis *(25)* to avoid the exclusion of a large proportion of case patients and controls from the analysis.

Results

Table 1 shows selected characteristics of the case patients and matched controls in the study and some characteristics of their initial breast tumors. Slightly more than half of the women developed their first breast cancer prior to 1960. The average age at diagnosis was 51 years. Thirty-eight percent of the patients were premenopausal at diagnosis, 53% were perimenopausal or postmenopausal, and 9% were of unknown

Table l. Characteristics of women with contralateral breast cancer (case patients) and their matched controls*

Characteristic	% case patients (n = 529)	% controls (n = 529)
Year of diagnosis		
Before 1950	22.7	23.1
1950-1959	32.5	31.8
1960-1969	31.8	32.3
After 1970	13.0	12.9
Age at diagnosis, y		
<45	19.1	18.2
45-54	39.3	39.5
>=55	41.7	42.3
Years of follow-up†		
8-9	23.8	—
10-14	35.5	—
15-19	20.8	—
20-24	11.0	—
>=25	8.9	—
Vital status follow-up, y		
8-9	4.0	1.7
10-14	22.7	15.7
15-19	26.7	22.5
20-24	21.6	21.7
>=55	25.1	38.4
Tumor stage		
Localized	54.1	54.1
Regional spread	9.6	6.6
Distant metastasis	0.2	0.8
Unknown	36.1	38.5
Tumor histology‡		
Carcinoma NOS	9.3	8.5
Adenocarcinoma NOS	73.0	72.8
Specified adenocarcinoma	14.4	17.2
Other specified	0.2	0.2
Unknown	3.2	1.3
Treatment		
Mastectomy	93.4	94.9
Lumpectomy	4.9	3.6
Oophorectomy	1.9	2.6
Radiation§	82.4	82.4
Chemotherapy		
Adjuvant	2.7	0.8
For recurrent disease	11.9	7.9
Endocrine therapy		
Adjuvant	0.8	1.1
For recurrent disease	18.5	10.6
Family history		
Yes ‖	10.8	6.4
No	42.2	40.3
Unknown	47.1	53.3
Reproductive history		
Nulliparous	23.8	18.5
Parous		
1-2 live born	32.3	39.3
3 + live born	21.2	22.3
No. unknown	3.8	2.1
Unknown if parous	18.9	17.8
Menopausal status		
Premenopausal	39.9	36.9
Perimenopausal	9.3	12.9
Postmenopausal	35.4	36.5
Radiation-induced menopause	1.5	1.5
Surgically induced menopause	4.9	3.4
Unknown	9.1	8.9
Age at menarche, y		
Known	41.6	39.7
Unknown	58.4	60.3
Height known	66.9	66.0
Weight known	55.2	63.9
Body mass index¶		
<20	3.2	5.5
20-24	25.1	32.3
25-29	16.6	16.8
>=30	6.4	5.1

menopausal status. More than 90% of case patients and controls were treated surgically with mastectomy, and 82% in each group received adjuvant radiotherapy. Recurrent disease was treated almost exclusively by chemotherapy and hormone therapy. Chemotherapy was given sporadically and included alkylating agents, predominantly cyclophosphamide. Prednisone was prescribed in most treatment regimens. One half of the patients who were given hormones received tamoxifen, some 30% received diethylstilbestrol, and the remainder received progesterone or androgens. The histology of the breast cancers was similar in case patients and controls.

If radiotherapy of the first breast cancer is a causal factor in the development of cancer in the second breast, one might predict that the second cancer would occur most frequently in the medial portion of the breast, since this area would receive the highest dose of radiation. To test this hypothesis, we compiled information on the anatomical position of the tumor in the contralateral breast from the available medical records. As shown in Table 2, the second tumors were evenly distributed in the medial, lateral, and central portions of the breast, a finding that argues against a causal role of radiotherapy in tumorigenesis. There appeared to be a slight tendency, however, for the second tumors to occur more centrally than the first.

Radiotherapy did not increase the overall risk for development of contralateral breast cancer (RR = 1.04; 95% CI = 0.74-1.46) (Table 3). The risk varied slightly with time since exposure and with age at exposure, but the findings were not statistically significant. Dose-response analyses were conducted for all patients combined and for patients grouped according to time since exposure and age at exposure. No trend in RR by radiation dose was seen with either parameter (Table 4). In general, our risk estimates were compatible with those obtained in a similar case-control study conducted in Connecticut; the latter results are shown for comparison in Table 3 and are discussed below.

Radiation therapy, hormone therapy, chemotherapy, menopausal status, body mass index, family history of breast cancer, and parity were evaluated simultaneously. Parity (RR = 0.67: 95% CI = 0.49-0.92) and premenopausal status (RR = 0.75; 95% CI = 0.52-1.07) appeared to protect against the development of contralateral breast cancer; however, the confidence limits were wide. Increasing body mass (body mass index = 25-29: RR = 1.37; 95% CI = 0.94-2.00; body mass index = >=30: RR = 1.77; 95% CI = 1.00-3.14) and family history of breast cancer (RR = 1.44; 95% CI = 0.89-2.34) appeared to be associated with elevated risks. Simultaneous adjustment for all factors, including the limited data on chemotherapy and hormones, had no effect on the estimate of radiation-associated risk.

* Tumor diagnosis, characteristics, and treatment are given for the first breast cancer.

† For case patients, this represents the interval between the date of first and second primary breast cancer. Controls were followed for the same time interval as the corresponding case patients.

‡ NOS = not otherwise specified.

§ For 16 case patients (3.0%) and 13 controls (2.5%), the radiotherapy status was unknown.

‖ Breast cancer was reported in first-degree relatives (mothers and sisters) of 48 (17.1%) of the case patients with known family history and in 29 (11.7%) of controls with known family history.

¶ Body mass index = (weight)/(height^2).

Discussion

The results of our case-control study indicate that radiation treatment of women with primary breast cancer does not significantly increase the risk for development of contralateral breast cancer. This finding was somewhat unexpected, since the estimated mean dose of radiation to the contralateral breast in this study (2.51 Gy) has been shown to be sufficient to cause breast cancer in other study populations *(1,2,4,5,26)*. The age at radiation exposure may be a critical factor, however. In practically all studies with positive findings, radiation-associated risk has been concentrated in young premenopausal women, most notably in women under age 30 years at time of exposure *(4)*. By contrast, the average age at radiation exposure in our series of patients was 51 years.

Other studies have suggested that the risk of radiogenic breast cancer decreases with increasing age at exposure. No increase in risk is seen in tuberculosis patients who have undergone multiple chest fluoroscopic examinations after about age 40 years *(4,27)*, and minimal risk is observed among atomic bomb survivors who were over age 40 years in 1945 *(1)*. Based on estimates of decreasing radiation effect with increasing age at exposure from other studies *(4)*, a dose of 2.51 Gy to the breast would have been predicted to result in an RR of only about 1.18. The confidence limits around our point estimate of 1.04 includes 1.18; thus, we cannot exclude the possibility of a small radiation-associated increase in risk.

The question arises as to why the results from this nested case-control study differ from those of the Danish registry cohort study *(19)*, in which a 30% increased risk of contralateral breast cancer was observed for irradiated versus non-irradiated patients 10 years or more after initial treatment. The explanation appears to be that the radiation treatments may have been misclassified in the cancer registry records used in the cohort analysis, particularly for patients with more than one cancer. In the present study, we were able to obtain more specific exposure information on case patients and controls and could evaluate the possibility of a radiotherapy effect more precisely. We did observe a differential misclassification of radiation treatment among case patients and controls in the registry records which, when corrected for (based on data obtained from the medical records), reduced the risk computed in the cohort study. The risk estimates from the two studies (1.04 versus 1.3) are not substantially different, but the absence of a dose-response effect leads us to conclude that radiation therapy has a minor role in the development of contralateral breast cancer.

We have carefully considered a number of factors that may have obscured the detection of radiation-associated risk in the present study but are confident in ruling them out. It is unlikely

Table 2. Anatomical position of tumor in women with unilateral breast cancer (controls) and in women with bilateral breast cancer (case patients)

	Controls		Case patients			
			First tumor		Second tumor	
Position in breast	No.	%	No.	%	No.	%
Medial, inner quadrants	130	32	116	32	124	34
Lateral, outer quadrants	162	40	135	37	122	33
Central, midline	117	29	113	31	121	33
Not stated	120	—	165	—	162	—

Table 3. RR of development of contralateral breast cancer after radiation treatment, according to time since treatment and age at treatment

	Denmark study		Connecticut study	
Parameters	RR	95% CI	RR	95% CI
All patients	1.04	0.74-1.46	1.19	0.94-1.50
Time since treatment, y				
<10*	0.83	0.36-1.93	0.99	0.68-1.43
10-14	0.93	0.52-1.66	1.98	1.29-3.06
>=5	1.23	0.74-2.03	0.93	0.62-1.40
Age at treatment, y				
<45	0.85	0.38-1.89	1.59	1.07-2.36
45-54	0.97	0.59-1.60	0.85	0.56-1.30
>=55	1.24	0.69-7.82	1.18	0.79-1.78

*In the Connecticut study *(35)*, this period is 5-9 years; in the Denmark study, it is 8-9 years.

Table 4. RR of development of contralateral breast cancer over five categories of radiation dose, according to time since treatment and age at treatment

	Estimated dose to the contralateral breast, cGy*						
Category	0	1-99	100-199	200-299	>=300	Unknown	*P* value†
All patients‡							
Average dose, cGY	0	52	151	250	462	—	
No. of case patients	77	28	66	163	61	134	
No. of controls	80	39	66	153	75	116	
RR	1.0	0.74	1.05	1.11	0.86	1.36	.91
95% CI							
Lower	—	0.41	0.66	0.75	0.54	0.59	
Upper	—	1.34	1.69	1.63	1.37	3.15	
RR by time since treatment, y							
8-14	1.0	0.52	1.36	1.00	0.61	0.93	.34
15-19	1.0	1.12	0.69	1.10	1.88	1.24	.32
>=20	1.0	1.15	0.88	1.28	1.16	1.03	.79
RR by age at treatment, y							
<45	1.0	0.86	0.78	1.15	0.54	0.75	.72
45-54	1.0	0.72	1.02	0.96	0.80	1.23	.40
>=55	1.0	0.66	1.32	1.31	1.09	1.42	.27

* The 16 case patients and 13 controls whose radiotherapy status was unknown were included in the analysis as a separate category (not shown).
† *P* value for trend (two-sided).
‡ Case patients and controls for whom dose information was missing or incomplete were excluded from the trend test.

that our results are due to chance, given the large number of case patients (n = 529) in the study and the proportion of these patients who received radiation therapy (>80%). It is also reasonable to rule out the possibility of aberrant results due to insufficient follow-up, since about 40% of the patients were followed for 15 years or more. Our estimates of radiation dose are unlikely to be in error by more than 20%-30%, an amount insufficient to account for the negative results. Selective destruction of records according to treatment status for the 51 case patients whose records were unavailable (which would have biased the estimate of radiation effect toward the null) seems unlikely, since the destruction of records was based on administrative decisions in certain hospitals.

Overmatching by age and calendar year could result in a concordance of exposure between case patients and controls. Radiotherapy for breast cancer has been a common and relatively standardized practice in Denmark for many years *(21)*. The range of breast doses (Table 4) experienced within matched pairs is broad (extending from no radiation to >6 Gy), however, and should have enabled us to discern an increasing risk with increasing dose if radiation treatment of the first primary breast cancer contributed to the risk of contralateral breast cancer.

To the extent that data were available in the medical records, there was no evidence of confounding of our estimate for radiation-associated risk by other known breast cancer risk factors *(28)*. In a multivariate analysis, nulliparity, obesity, and family history of breast cancer were all found to increase the risk of contralateral breast cancer, without any change in the estimate of radiation-associated risk. Our data on adjuvant chemotherapy and endocrine treatment were too incomplete to provide reliable information on whether these treatments protect against the development of contralateral breast cancer, as suggested in other studies *(29-34)*.

Our findings are supported by the results of a similar case-control study *(35)* of women in Connecticut. This study involved 655 women with contralateral breast cancer. The main results of the present study and of the Connecticut study are compared in Table 3. A slightly increased overall risk of radiogenic breast cancer (RR = 1.19) was reported in the Connecticut study, compatible with our estimate of 1.04. Apart from a risk elevation for follow-up years 10-14 in Connecticut and an elevated risk among patients exposed to radiation under the age of 45 years, the results of the two studies are remarkably similar. The similarity is noteworthy, given the differences in the proportion of patients receiving radiotherapy in the two studies (22% of patients in the Connecticut study versus 82% in the Denmark study). It is also noteworthy that the radiation-associated risk in the Connecticut study was concentrated entirely among women exposed under age 45 years. We may have been unable to detect excess risk in women under age 45 years in the present study because fewer women in our series were in this age category (101 patients in our study versus 200 in the Connecticut study). This difference in age distribution may also explain the slightly higher overall risk estimate for radiogenic breast cancer in the Connecticut study.

Both studies are firm, however, in that women exposed at and after the age of 45 years to several grays are at minimal (if any) risk of radiogenic breast cancer. The reason(s) that breast tissue of postmenopausal women appears less susceptible to the carcinogenic force of ionizing radiation is not entirely clear, but it maybe related to hormonal events. Radiation is generally considered to be a tumor initiator. Conceivably, radiation exposure at a young age could cause mutational damage which, in conjunction with appropriate promotional stimuli in later life, would lead to the development of breast cancer. Such promotional stimuli may be linked to menstrual cycles, pregnancy, and perhaps exposure to exogenous estrogens. In contrast, radiation exposure after menopause would typically not be followed by these hormonal influences and therefore may not lead to the development of breast cancer. Although these ideas are speculative, we believe that the relatively advanced age at exposure of our study population is the primary reason that we did not detect a radiation-associated increase in risk.

The results of both the Denmark and the Connecticut studies are relevant to current treatment practices for breast cancer patients and to screening programs of asymptomatic women for the early detection of breast cancer. It is unlikely that breast-conserving surgery with adjuvant radiotherapy will result in detectable increases in breast cancer. Not only are most women diagnosed with breast cancer over the age of 45 years, but also current radiotherapy techniques result in much lower doses to the contralateral breast than in the past. Nevertheless, while unnecessary radiation exposure to the contralateral breast should be avoided for women of all ages, particular caution should be exercised in the case of women under age 45 years.

In Denmark, mammographic screening for breast cancer is recommended for women over the age of 50 years. A mammographic screening exposes the breast to an average dose of less than 0.005 Gy; thus, mammographic x rays every year for 20-30 years would rarely result in a cumulative breast dose that even approached 1 Gy. Our findings should be reassuring in that no risk of radiogenic breast cancer was apparent at doses from 1 to 6 Gy when women were exposed at and after the age of 45 years. Women with multiple breast cancer risk factors have been recommended as ideal candidates for mammographic screening, but there is some concern that radiation might act synergistically with these predisposing factors to greatly enhance the risk of subsequent breast cancer. Again, women with breast cancer are at very high risk (over twofold to fivefold) for developing a second breast cancer, but this heightened risk appears independent of radiation exposure. Age at exposure appears to be the most important predictor of future risk, with exposure at and after age 45 years having minimal risk.

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